Metabolism/Biotransformation

Introduction

Metabolism is the term that is most commonly used to refer to this stage of a drug's life cycle. "Metabolism" is often perceived by students to be associated with the processing, breaking down, or inactivating of a drug. However, that association is misleading—**biotransformation** is a better word. **Biotransformation means, "make more water soluble."** It does NOT mean make less active, it does NOT mean degrade, it does NOT mean anything other than "make more water soluble." Metabolism and biotransformation are interchangeable words, but biotransformation leaves the learner with only the medical sense of the word. But because either or both are used in different texts, this lesson will purposefully flip between metabolism and biotransformation. We want you to associate these two words as being the same process.

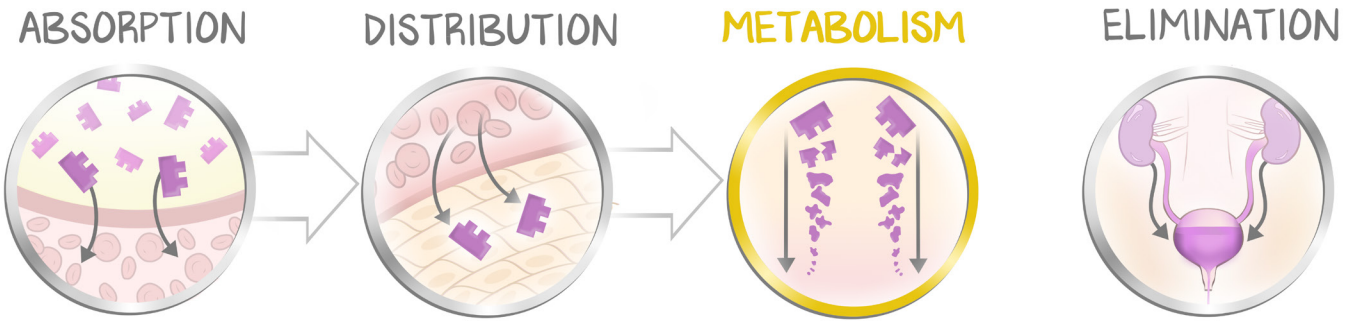

Figure 4.1: Pharmacodynamic Map, Metabolism

The pharmaceutical industry, as manufacturers of pharmaceuticals, attempt to make things small, nonpolar, and lipid soluble to ensure that more gets absorbed, and more gets distributed. Our bodies identify those pharmaceuticals as toxins and attempt to make those drugs more water soluble, larger, polar, so as to facilitate their elimination through the urine, which is made of water. We get the drug in; our body gets the drug out.

Metabolism Changes the Function of the Drug

Drugs we administer are not necessarily the active compound. When a drug is metabolized, changed to be more water soluble, a new compound is made. That new compound can be active or inactive, or be active in a whole different way. There can be the drug as we administer it (the drug), the metabolic step (metabolism), and the resultant molecule (metabolite). Which means that **"changing"** can have three outcomes.

	STARTING COMPOUND		RESULTANT COMPOUND
Inactivation	Active drug	Metabolism	Inactive drug
Activation	Inactive prodrug	Metabolism	Active drug
Alteration	Active drug	Metabolism	Active metabolite

Table 4.1: Results of Biotransformation
Biotransformation takes the original compound and makes it more water soluble, resulting in a new compound. The original compound can be an inactive prodrug or an active drug. The resultant compound can be an inactive metabolite or the active compound made from the prodrug, or the metabolite can be active in another way altogether.

Inactivation occurs when the body takes an active compound and makes it not work anymore. This is what most people think of as metabolism.

Activation occurs when the body takes something that doesn't do anything in its current form (the **prodrug**), and lets it metabolize into the active drug. This is done when the active drug is a poor pharmaceutical—when the active compound is poorly absorbed, poorly distributed, or quickly metabolized. By giving the prodrug, we can enhance delivery of the compound we actually want. This also allows us to give a nontoxic prodrug that will only be activated by cells with certain machinery—such as cells infected with a virus. Only the virally infected cells will activate the drug and die, while all other cells will see only the inactive prodrug and be left unaffected.

Alteration occurs when the body processes drugs in ways that lead to unanticipated toxic compounds. The body sees a foreign compound and uses whatever it has to metabolize it. The body certainly hasn't developed enzymes to silence pharmaceuticals, so whatever is close enough is what it uses. In doing so, it may create something toxic. This is of particular consequence with **toxic metabolites**. What causes problems isn't the compound the patient took, but rather what metabolism does with it.

The concept of a toxic metabolite is well represented by **ethylene glycol**. Ethylene glycol is a component in antifreeze, which, when consumed, works like **ethyl alcohol**—the patient gets drunk. The problem isn't the ethylene glycol (it isn't good for people, but it isn't dangerous), but rather the metabolite that gets made from its metabolism: **glycolaldehyde**. The **hydrolysis** of ethylene glycol results in glycolaldehyde. **Alcohol dehydrogenase** (the same enzyme that metabolizes ethyl alcohol) is the enzyme that hydrolyzes ethylene glycol to glycolaldehyde. If glycolaldehyde accumulates, it causes renal failure and death.

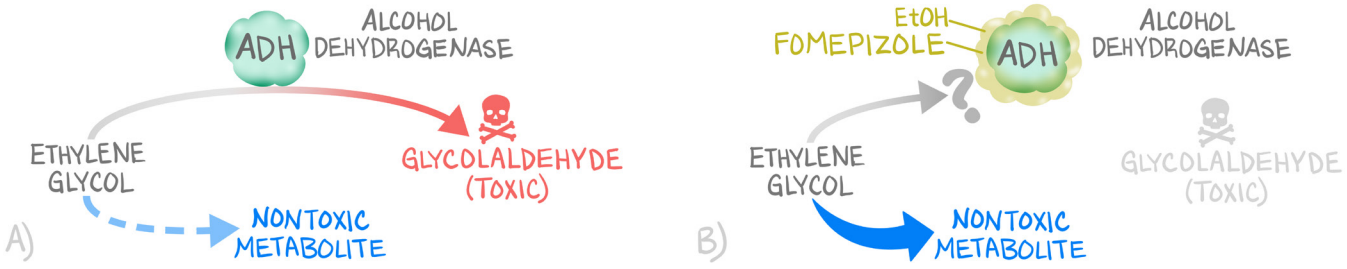

Figure 4.2: Ethylene Glycol and Alcohol Dehydrogenase
(a) Ethylene glycol is metabolized by alcohol dehydrogenase into glycolaldehyde. The original "drug" ethylene glycol gets the patient drunk. The biotransformation to glycolaldehyde, the active metabolite, leads to renal failure and death. (b) Alcohol dehydrogenase has a higher affinity for alcohol than for ethylene glycol. Coadministration of EtOH to a patient with ethylene glycol toxicity saturates alcohol dehydrogenase, and ethylene glycol is metabolized by other enzymes into nontoxic metabolites.

Ethylene glycol is metabolized by alcohol dehydrogenase. Alcohol dehydrogenase works on many alcohols. If someone drinks ethylene glycol, the toxic metabolite accumulates because of alcohol dehydrogenase. If ethylene glycol is around and alcohol dehydrogenase is busy doing something else, that toxic metabolite doesn't accumulate. Alcohol dehydrogenase would be "busy doing something else" if there were another alcohol present for which there was a higher affinity for alcohol dehydrogenase. The treatment for ethylene glycol intoxication is **fomepizole**, which inhibits alcohol dehydrogenase, thereby preventing the accumulation of toxic metabolites.

But it just so happens that administering **EtOH**, for which alcohol dehydrogenase has a much higher affinity, can prevent ethylene glycol metabolism. **Acute alcohol consumption** causes **competitive inhibition** of hepatic enzymes, leaving the metabolism of other compounds inhibited. In the case of ethylene glycol toxicity, this is a good thing. We will see how alcohol has other effects on hepatic metabolism of drugs in the acute and chronic state later this lesson, in the section on CYP450.

Metabolism Makes Molecules Hydrophilic in Two Phases

The phases are not necessarily sequential. The second phase can occur without the first, if there's already an exposed polar group. The first phase exposes a polar group for the second phase to act on. Since most drugs are constructed to be nonpolar, you should learn metabolism as phase 1 then phase 2, in order, consecutively.

Phase 1 is mitigated by **cytochrome P450** enzymes in **hepatocytes**. Phase 1 is designed to take a large molecule that is hydrophobic, and, through an **irreversible alteration** of the drug, to add or reveal a polar group.

Polar groups are **hydroxyl** (-OH), **sulfa** (-SH), **amine** (-NH_3^+), and **carboxyl** (-COO^-). The process that results in an exposed polar group is **irreversible**. Those metabolites may still be worked on, being further metabolized, but there's no going back. Now, while we did say "metabolism means make more polar, not inactivate," the purpose of metabolism's making molecules more polar is so they can **be more easily eliminated** , especially in the urine. So while we, the manufacturers of drugs, attempt to maximize distribution of our meds (small, nonpolar, lipophilic, not bound to albumin), the body is taking whatever we give it, and undoing it. The body's goal is to make it **large, polar, hydrophilic**, and bound to albumin.

Phase 1 is a good start, as it adds or exposes a polar group, making the drug more water soluble. But the process usually adds only one small polar piece. And it would be inefficient to continually chop apart smaller and smaller metabolites just to add one more polar group. Instead, **phase 2** takes the smaller pieces, uses that exposed polar group from phase 1, and then adds **large, very polar compounds**. This step is **reversible**, induces **no conformation change**, and is called **conjugation**.

Conjugation occurs most commonly in the form of **glucuronidation** (UDP-GT), but also by acetylation, sulfation, and glutathione conjugation.

Take for example the metabolism of aspirin. Aspirin undergoes **hydrolysis** (phase 1) by **CYP450 enzymes** to salicylic acid. Phase 1, irreversible, adds one -OH, one small polar end. Then, under the influence of **UDP-glucuronyl transferase** (this comes up in bilirubin metabolism, so start saying the word out loud so the name sticks), that salicylic acid is tagged, at the -OH that was just created by phase 1, with a **massive and very polar** molecule rich in exposed hydroxyl groups. The **many hydroxyl groups** make this new "tagged" molecule **much more water soluble** and **much larger**. If this metabolite is already in the urine or, in the case of bilirubin, already in the water-filled cystic duct, then the metabolite becomes trapped, and is eliminated with the rest of the fluid.

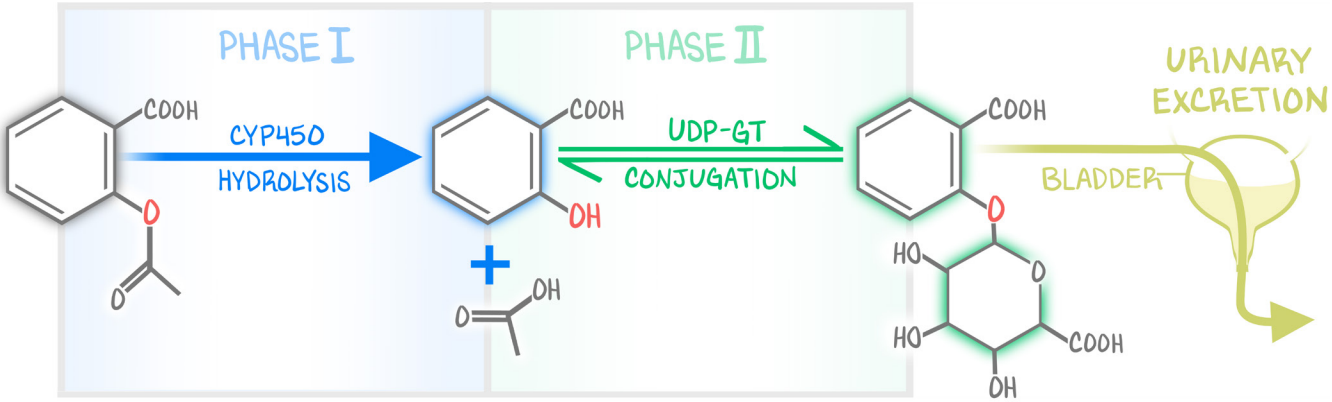

Figure 4.3: Aspirin Metabolism
CYP450 enzymes are responsible for Phase 1 metabolism; in this instance it is hydrolysis. Hydrolysis causes an irreversible cleaving of the molecule, leaving an exposed hydroxyl group. In this process, UDP-glucuronyl transferase is responsible for Phase 2 metabolism and involves a conjugation step. It takes the very polar, very large, 6-carbon structure and adds it to the single hydroxyl group created by the phase 1 step.

I like to think of the relationship of phase 1 and phase 2 like this. Phase 1 is a samurai—heavily armored, years of training, with great weaponry. There's a ninja hiding in a crate. Phase 1 uses the heavy sword to cut open the box, exposing the ninja. Phase 2 is the townsfolk the samurai is defending, who now swarm the ninja with pitchforks and rolling pins, defeating him.

Much Ado about CYP450

These enzymes are sexy and are a hot topic for the boards—and for your patients. The problem is that there are **so many CYP450** enzymes, that it becomes impossible to keep them straight. They are named by a number, subclass letter, and subclass number. Multiple CYP450 enzymes will metabolize one drug, and multiple drugs will be metabolized by the same CYP450 enzyme. We've cataloged some that are important, but we just don't have the information yet to know how to predict all drug interactions. Suffice it to say that memorizing the letter-number name of a drug isn't worth the effort. But knowing some key concepts about a selective few will help.

Cytochrome P450 enzymes can be **induced** or **inhibited**. Alcohol illustrates both concepts. **Acute alcohol inhibits** cytochrome P450 enzymes, thereby decreasing the biotransformation of other medications (causing them to accumulate). With **chronic alcohol consumption**, when alcohol has always been around inhibiting the P450s, the liver feels the absence of those cytochrome P450 enzymes, so increases the number of P450 enzymes. Those who consume alcohol chronically generally can **process drugs** (and alcohol) **faster** than others because they have induced cytochrome P450 enzymes.

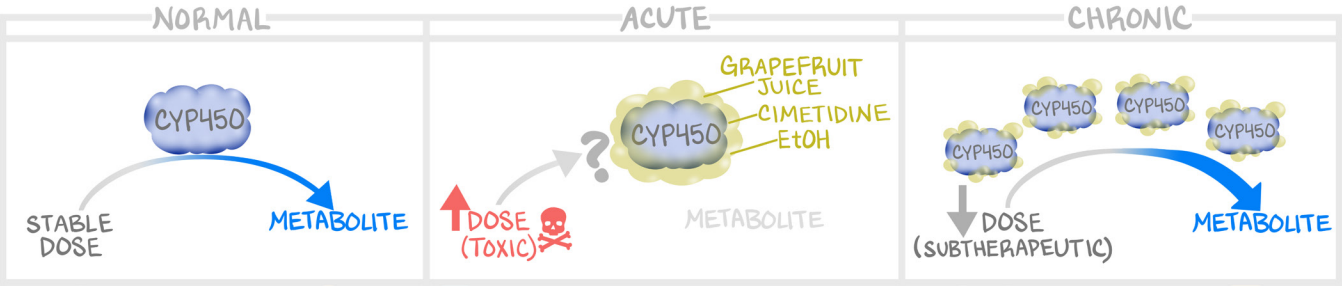

Figure 4.4: Acute vs. Chronic Alcohol on CYP450 Enzymes
Acute alcohol consumption inhibits CYP450 enzymes, decreasing metabolism of drugs, leading to the accumulation of toxic levels of medications. The liver does not have time to compensate with more enzymes. If the alcohol is stopped, the normal metabolism resumes. The liver responds to chronic alcohol consumption by upregulating the CYP450 enzymes, thereby increasing the metabolism of drugs, reducing their efficacy. Having been chronically inhibited, the liver has time to compensate with more enzymes.

Other classic CYP450 inhibitors include **cimetidine** and **grapefruit juice**. Both inhibit cytochrome P450-34A, reducing the metabolism of drugs that 34A clears. Statins are metabolized by 34A. Taking cimetidine or grapefruit juice with a **statin** will decrease the metabolism of the statin, causing accumulation of the drug, leading to toxic side effects (elevation of liver enzymes, weakness, and an elevated marker of muscle damage, CPK). And this is **not a class effect**—only cimetidine causes this problem, not other H_2-blockers. So while cimetidine is never prescribed anymore, it still makes its way onto testing.

Enzyme genetics play a role as well. **Warfarin** is used to treat clots. It's biotransformed by **CYP450-2C9**. 2C9 also metabolizes phenytoin. This particular CYP450 enzyme is vulnerable to genetic polymorphisms—some people are **slow acetylators** (metabolizing much more slowly than the average) and need much less dosage to achieve the same effect, while others are **fast acetylators** (metabolizing much faster than the average), and will chew through massive doses of warfarin without any change in their clotting-factor studies. This is why some patients may be on only 2.5 mg of warfarin every other day, and others 10 mg daily.